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A STUDY OF PHYSIOLOGICAL MECHANISMS AND INTER-RELATIONS BETWEEN SYSTEMIC AND REGIONAL BLOOD VOLUME BLOOD FLOW AND ELECTROLYTE BALANCE

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(1) Regulation of Sodium Excretion

a) Effects of Fasting and Refeeding

Previous studies established that the ingestion of carbohydrate induces an antinatriuresis only after starvation. Studies to determine whether the effects of glucose ingestion on the excretion of other uni-and divalent ions were also dependent upon the metabolic set and to determine the tubular sites where carbohydrate exerts its sodium-retaining effects were undertaken. Healthy volunteers were equilibrated on a 1500 calorie diet and maintained on a constant intake of sodium, potassium, and fluid throughout the study. To assure adequate urine flow and inhibit the release of antidiuretic hormone, a water diuresis was induced in each subject in the equilibrated state and again after three days of starvation. Oral glucose given in the fed state did not alter sodium excretion ($U_{Na}V$), but mean calcium and phosphate excretion rose significantly ($p < .02$ in both instances), while urine potassium fell ($p < .02$). After starvation oral carbohydrate affected calcium, phosphate and potassium as in the fed state, but a significant fall in mean $U_{Na}V$ occurred.

During water diuresis in starvation, sodium loss was accompanied by a fall in the ratio of free water clearance/volume, indicating a decreased reabsorption of Na at the diluting segment. The antinatriuresis that followed oral glucose was accompanied by a decrease in the ratio of urine volume/100 ml glomerular filtration rate, suggestion that the increased Na reabsorption occurred in the proximal tubule.

The studies indicate that: 1) the effects of oral glucose on sodium excretion are dependent upon metabolic conditions while those on potassium, calcium and phosphate are independent of these conditions; 2) specific tubular sites involved in sodium reabsorption are influenced by the metabolic set; and 3) the secretion of potassium and urinary titrable acidity may be independent of sodium excretion.

b) Effects of Atrial Arrhythmias upon Cardiac and Renal Function

In a previously described study of both renal and cardiac hemodynamics in 11 dogs during normal sinus rhythm, atrial pacing and atrial fibrillation, at comparable rates, both atrial tachycardia and atrial fibrillation were found to be associated with significant decreases in arterial blood pressure, renal blood flow and sodium excretion. Changes in urinary sodium excretion correlated best with changes in blood pressure ($r=+0.84$).

These observations supported previous work suggesting that arterial perfusion pressure is the prime link between systemic hemodynamics and sodium excretion.

In these experiments, reversion to regular sinus rhythm failed to be accompanied by full recovery of systemic and renal hemodynamics and sodium excretion. Persistent depression of blood pressure and sodium excretion could be related either to deterioration of the model with time or possibly to a residual affect of the tachyarrhythmia. To investigate these possibilities, two experiments have been initiated: shorter studies starting with induced tacharrhythmia, and prolonged sham studies. Preliminary results suggest that the above post-tachyarrhythmic effects cannot be attributed to deterioration of the model.

This post-arrhythmia hemodynamic depressive effect may explain the failure of several human studies to demonstrate early hemodynamic benefit from cardioversion, as well as the persistence of heart failure in some patients after transient bouts of tachyarrhythmia.

(2) Further Development and Application of Fiberoptic Catheter Systems for the Measurement of Intravascular Pressure.

The development of fiberoptic catheter systems for the recording of intravascular pressures and sound and their use in large laboratory animals and in man have been described in previous reports. This system, with minor modifications, has permitted the study of hemodynamics of small rodents.

a) Normal Ventricular Pressures in the Mouse

Right and left ventricular pressures were measured simultaneously in 25 adult C3H mice, under pentobarbital anesthesia, by means of percutaneous ventricular punctures with 26 gauge hypodermic needles to which the fiberoptic system was attached. The following values were obtained:

		Mean	SEM
Heart Rate	beats/min	587	10
Left Ventricular pressure, systolic	mm Hg	102	3
Left Ventricular pressure, end-diastolic	mm Hg	3	0.4
Right Ventricular pressure, systolic	mm Hg	21	1
Right Ventricular pressure, end-diastolic	mm Hg	1	0.3

To our knowledge, these represent the first such measurements.

b) Hemodynamic Study of Biventricular Failure in Experimental Chagasic Myocarditis

It has been noted that clinical heart failure in primary myocardial diseases affecting both ventricles tends to manifest as predominant right ventricular failure. The pathogenetic mechanism of this phenomenon has never been adequately explained. The above method was used to approach this question in experimental acute Chagasic (Trypanosoma cruzi) myocarditis induced in the C3H mouse, associated with right ventricular dilatation and congestive heart failure. Measurements in 25 infected animals, age-matched to the above control animals, revealed the following:

		Mean	SEM
Heart Rate	beats/min	504	20
Left Ventricular pressure, systolic	mm Hg	82	4
Left Ventricular pressure, end-diastolic	mm Hg	7	0.5
Right Ventricular pressure, systolic	mm Hg	21	1
Right Ventricular pressure, end-diastolic	mm Hg	7	0.4

Compared to healthy control mice (v.s.), in the mice with myocarditis, heart rate and left ventricular systolic pressure were lower, left and right ventricular end-diastolic pressures were higher (all differences significant at $P < 0.001$), and right ventricular systolic pressure was unchanged. The ratio right ventricular systolic pressure/left ventricular systolic pressure was increased by 25 per cent. Thus, whereas the left ventricular pressure load was decreased, right ventricular pressure load remained unchanged and hence relatively greater than the former. The mechanism of clinical dominance of right ventricular failure in the presence of physiological biventricular failure appears thus clarified.

(3) Chronotropic Augmentation of Cardiac Function in Experimental Myocardial Infarction.

Whereas other work under this grant has revealed undesirable circulatory effects of tachyarrhythmias, one situation has been studied in which rapid pacing was found to be beneficial.

Previous experiments in this laboratory have demonstrated that left ventricular function is depressed one week after experimental myocardial infarction in the dog. In six unanesthetized dogs, whose left anterior descending coronary artery had been occluded previously, measurements of heart rate, cardiac output, mean aortic pressure and left ventricular diastolic pressure were made before and during atrial pacing at 180 beats/min. Cardiac output increased from 3.1±0.3 L/min (SEM) and left ventricular end-diastolic pressure decreased form 18±2 mm Hg to 9±1 mm Hg ($P < 0.05$), while aortic pressure remained unchanged.

In two additional animals with previous occlusion of the left anterior descending artery, more severe left ventricular failure was induced by partial constriction of the circumflex artery. One developed acute pulmonary edema which resolved with atrial pacing at 180 beats/min. Cardiac output rose from 3.2 to 3.7 L/min and left ventricular end-diastolic pressure fell from 34 to 17 mm Hg.

These studies indicate that left ventricular failure in experimental myocardial infarction may be accompanied by a less than optimal chronotropic response, and that an increase in the sinus rate may have therapeutic effects. These findings may have clinical applications.

Publications

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